L35 ANSWER 148 OF 272 HCAPLUS COPYRIGHT 2006 ACS on STN
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DOCUMENT NUMBER: 124:176952
TITLE: Preparation of cyclosporin phosphoric acid esters as immunosuppressants
INVENTOR(S): Konno, Kyotaka; Seto, Takashi; Yoshifusa, Hiroto; Ezure, Yoji
PATENT ASSIGNEE(S): Nippon Shinyaku Co Ltd, Japan
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CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
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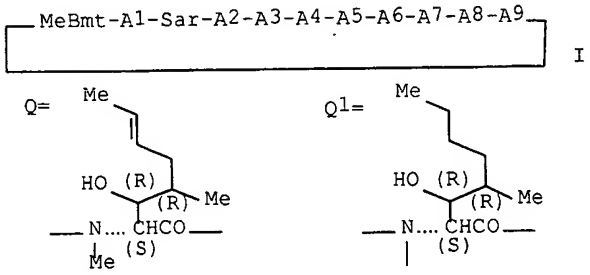
OTHER SOURCE(S): MARPAT 124:176952
GI



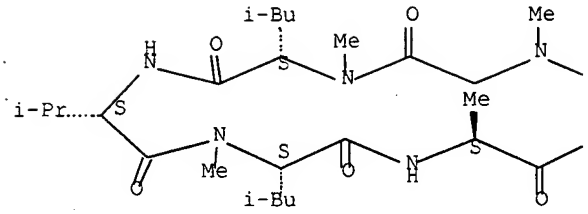
AB Cyclosporins consisting of HO-contg. amino acids in which part or all of the HO groups phosphonated, are prepared and have high water solubility, good intestinal absorption in oral administration, and reduced kidney toxicity, and are in vivo converted into potent nonphosphate form. The prefered cyclosporins are represented by general formula [I; A1 = D- or L-α-aminobutyric acid, D- or L-Ala, -Thr, -Val, or -hydroxyvaline; A2 = D- or L-MeLeu, -Leu, or -Val; A3 = D- or L-Val or -norVal; A4 = D- or L-Leu or -MeLeu; A5 = D- or L-Ala or -α-aminobutyric acid; A6 = D- or L-Ala or -Ser; A7, A8 = D- or L-MeLeu or -Leu; A9 = D- or L-Val or -MeVal; MeBmt = N-methyl-(4R)-4-buta-2E-en-1-yl-4-methyl-L-threonine Q or its dihydro form Q1]. Thus, 74 mg 2-cyanoethyl phosphonate, 204 mg DCC, and 4 mL pyridine were added to [D-serine8]cyclosporin A, and the resulting mixture was stirred 64 h, treated with 0.5 mL H2O, stirred for 30 min, filtered to remove the insol. matter, concentrated in vacuo to dryness, treated with 25% aqueous NH3, stirred for 21 h, filtered to remove the insol. matter, concentrated in vacuo to dryness, treated with 0.7 mL 0.5 N aqueous NaOH, stirred for 20 h, and after evaporating the solvent, adsorbed on a reversed phase C1-8 resin (MEGA BOND ELUT C1-8 cartridge, Analytichem). After washing the cartridge with water, it was eluted with 40% MeOH to give 70 mg [phosphono-D-serine8]cyclosporin A disodium salt (II.2Na). II showed IC50 of 19 ng/mL for inhibiting the production of interleukin-2 in Jurkat cell (human T-cell tumor cells) as compared to 3 ng/mL for cyclosporin A. The solubility of II.2Na in H2O was >500 mg/mL vs. 0.0267 mg/mL for cyclosporin A. In lithium clearance assay using rats, II.2Na showed very low kidney toxicity, whereas cyclosporin A showed kidney toxicity. Tablet, injection, and capsule formulations containing II.2Na were formulated.

IT **173946-64-0P 173946-65-1P 173946-66-2P**
174062-41-0P 174062-42-1P 174062-43-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of cyclosporin phosphoric acid esters as immunosuppressants)

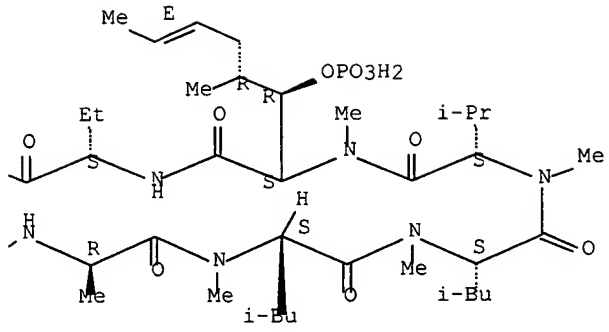
RN 173946-64-0 HCAPLUS
CN Cyclosporin A, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

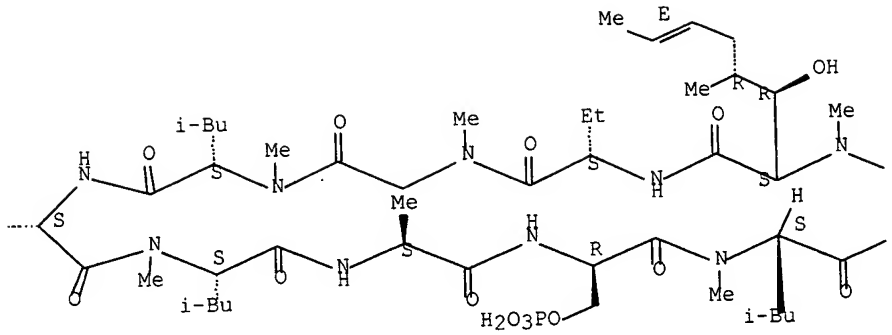


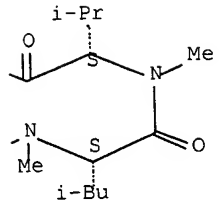
RN 173946-65-1 HCAPLUS
CN Cyclosporin A, 2-(O-phosphono-D-serine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

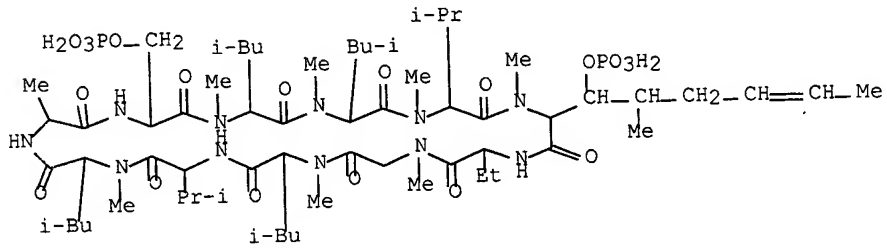
PAGE 1-A

i-Pr





RN 173946-66-2 HCAPLUS
CN Cyclosporin A, 2-(O-phosphono-D-serine)-, dihydrogen phosphate (ester), tetrasodium salt (9CI) (CA INDEX NAME)



●4 Na

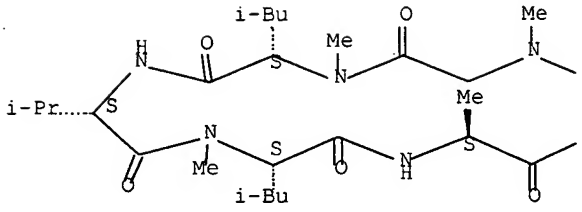
RN 174062-41-0 HCAPLUS
CN Cyclosporin A, dihydrogen phosphate (ester), disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

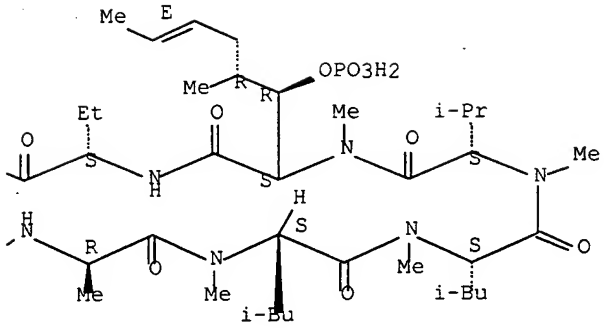
PAGE 1-A

●2 Na

PAGE 1-B



PAGE 1-C



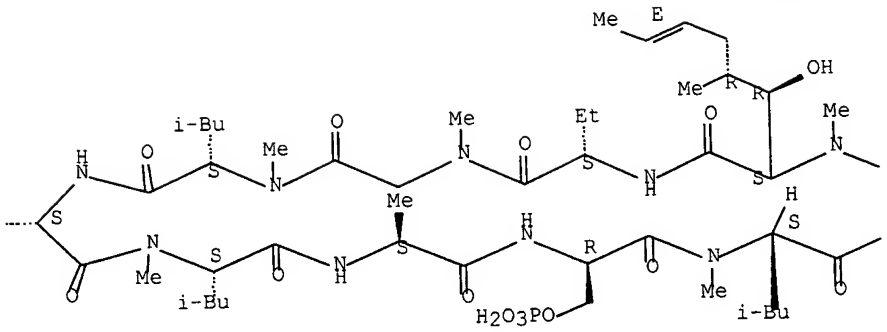
RN 174062-42-1 HCAPLUS
CN Cyclosporin A, 2-(O-phosphono-D-serine)-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

i-Pr

PAGE 1-B



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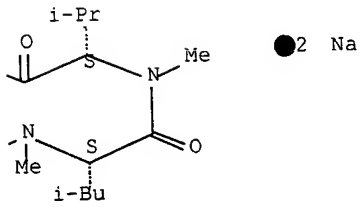


RN 174062-43-2 HCAPLUS
CN Cyclosporin A, 2-(O-phosphono-D-serine)-, compd. with benzenemethanamine (1:2) (9CI) (CA INDEX NAME)

CM 1

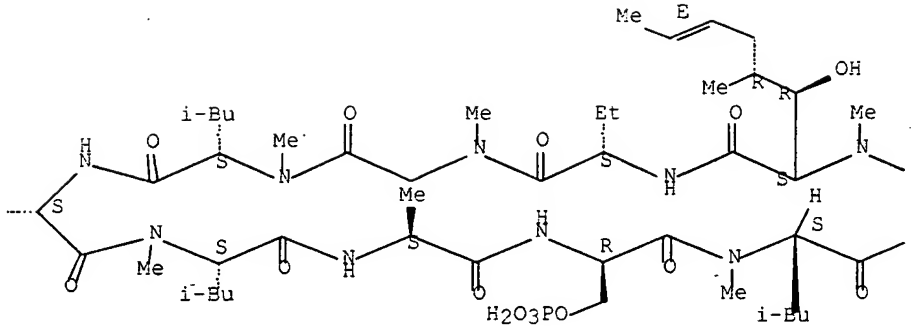
CRN 173946-65-1
CMF C62 H112 N11 O16 P

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

i-Pr

PAGE 1-B



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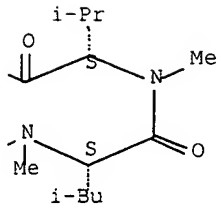

CM 2

CRN 100-46-9
CMF C7 H9 N

H_2N-CH_2-Ph